

10/043,268

(FILE 'HOME' ENTERED AT 12:39:27 ON 01 JUN 2004)

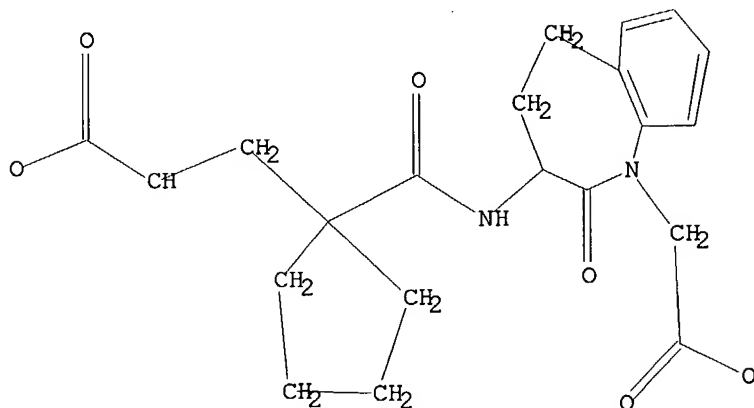
FILE 'REGISTRY' ENTERED AT 12:39:45 ON 01 JUN 2004

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 12:40:11 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS  
SEARCH TIME: 00.00.01

0 ANSWERS

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 3 TO 163  
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 12:40:17 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 78 TO ITERATE

100.0% PROCESSED 78 ITERATIONS  
SEARCH TIME: 00.00.01

60 ANSWERS

L3 60 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

155.42

155.63

FILE 'CAPLUS' ENTERED AT 12:40:22 ON 01 JUN 2004

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FILE COVERS 1907 - 1 Jun 2004 VOL 140 ISS 23  
FILE LAST UPDATED: 31 May 2004 (20040531/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3  
L4 8 L3

=> d 1-8 bib abs

L4 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:660247 CAPLUS  
DN 139:169370  
TI Immediate-release pharmaceutical formulation with enhanced bioavailability  
IN Gorissen, Henricus R. M.  
PA Solvay Pharmaceuticals B.V., Neth.  
SO PCT Int. Appl., 23 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068266	A1	20030821	WO 2003-EP50014	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1336414	A1	20030820	EP 2002-75623	20020214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRAI EP 2002-75623 A 20020214

OS MARPAT 139:169370

AB The present invention relates to an immediate release formulation with enhanced bio-availability comprising a solid homogeneous and thermostable solution of a poorly water-soluble biol. active substance, characterized in that

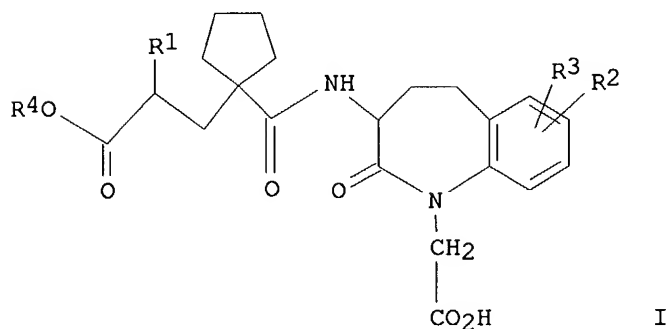
the solid solution comprises: (a) the active substance in an amount of between 10 and 50% of the total weight of the formulation, (b) a nonionic hydrophilic surfactant ingredient, which is in the liquid form between 15° and 30°C, in an amount of between 20% and 70 % of the total weight of the formulation and (c) a pharmaceutically acceptable organic polymer or mixture of

polymers, which polymer or mixture of polymers is in a liquid form above 60°C and in a solid form below 30°C, in an amount of between 5% and 70% of the total weight of the formulation, and (d) optionally comprises a disintegrating agent in an amount of between 1% and 10% of the total weight of the formulation. The invention further relates to active substances formulated into the above form and methods for producing the formulation. For example, capsules containing 3-[[[1-[(2R)-2-(ethoxycarbonyl)-4-phenylbutyl]cyclopentyl]carbonyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid Ca salt 103.7, Tween 80 311, and PEG-6000 234 mg per each, were formulated.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:571009 CAPLUS  
DN 139:138736  
TI Solid benzazepine salts preparation for pharmaceuticals  
IN Van Der Eerden, Joris A.; De Jong, Paulus P. g.; Van Der Meij, Paulus F. C.  
PA Solvay Pharmaceuticals B.V., Neth.  
SO PCT Int. Appl., 16 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003059939	A1	20030724	WO 2003-EP515	20030115
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	EP 2002-75621	A	20020116		
	NL 2002-1019762	A	20020117		
OS	MARPAT 139:138736				
GI					



AB The present invention relates to benzazepine salts and bivalent metal ion salts such as magnesium, calcium and zinc salts. Also pharmaceutical

compns. comprising the salts can be used in the treatment of hart disorders or hypertension, in the improvement of gastrointestinal blood flow or in the treatment and prophylaxis of cardiac damages induced by adriamycin and comparable anti-cancer drugs. Salts of I prepared include, Ca, Mg, Zn, Li, K, and Na and the S- $\alpha$ -methylbenzylamine salt which is useful as an intermediate in the production of the above mentioned salts.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:363526 CAPLUS  
DN 139:94628  
TI SLV-306 Solvay  
AU Tabrizchi, Reza  
CS Faculty of Medicine Basic Medical Sciences Health Sciences Centre,  
Memorial University of Newfoundland, St John's, NF, A1B 3V6, Can.  
SO Current Opinion in Investigational Drugs (Thomson Current Drugs) (2003),  
4(3), 329-332  
CODEN: COIDAZ; ISSN: 1472-4472  
PB Thomson Current Drugs  
DT Journal; General Review  
LA English  
AB A review. SLV-306 is an orally active mixed neutral  
endopeptidase/endothelin converting enzyme inhibitor under development by  
Solvay SA for the potential treatment of essential hypertension and  
congestive heart failure. The compound is currently undergoing phase II  
clin. trials in Belgium.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2002:304371 CAPLUS  
DN 138:49186  
TI SLV-306  
AU Sorbera, L. A.; Leeson, P. A.; Castaner, J.  
CS Prous Science, Barcelona, 08080, Spain  
SO Drugs of the Future (2002), 27(1), 27-31  
CODEN: DRFUD4; ISSN: 0377-8282  
PB Prous Science  
DT Journal; General Review  
LA English  
AB A review. The synthesis, pharmacol. actions, and clin. studies of  
SLV-306, a new drug for treating hypertension, is described. SLV-306 is  
synthesized by acylation of 3(S)-amino-2-oxo-2,3,4,5-tetrahydro-1H-1-  
benzazepine-1-acetic acid tert-Bu ester with 1-[2-(R)-(ethoxycarbonyl)-4-  
phenyl-butyl]cyclopentanecarboxylic acid by methanesulfonyl chloride and  
triethylamine in dichloromethane to yield the amide (III), which is then  
treated with trifluoroacetic acid to eliminate the tert Bu ester group.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2001:50486 CAPLUS  
DN 134:105881  
TI Pharmaceuticals with protective effects against oxidative-toxic  
substances, particularly against cardiotoxic substances  
IN Rozsa, Zsuzsanna; Papp, Julius G.; Thormahlen, Dirk; Waldeck, Harald  
PA Solvay Pharmaceuticals G.m.b.H., Germany  
SO PCT Int. Appl., 28 pp.  
CODEN: PIXXD2  
DT Patent  
LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001003699	A1	20010118	WO 2000-EP6525	20000710
	W: AU, BR, CA, CN, CZ, DZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RU, SK, TR, UA, US, ZA				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19932555	A1	20010118	DE 1999-19932555	19990713
	BR 2000012442	A	20020402	BR 2000-12442	20000710
	EP 1200095	A1	20020502	EP 2000-947960	20000710
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
	TR 200200053	T2	20020521	TR 2002-200200053	20000710
	JP 2003504336	T2	20030204	JP 2001-508979	20000710
	NO 2002000132	A	20020312	NO 2002-132	20020111
	ZA 2002000265	A	20030113	ZA 2002-265	20020111
	US 2003040512	A1	20030227	US 2002-43268	20020114
PRAI	DE 1999-19932555	A	19990713		
	WO 2000-EP6525	W	20000710		

OS MARPAT 134:105881

AB The invention relates to the utilization of benzazepine-N-acetic acid derivs. which contain an oxo group in addition to the nitrogen atom in the  $\alpha$ -position and which are substituted in the third position by a 1-(carboxyalkyl)cyclopentylcarbonylamino group and to their salts and biolabile esters for the prophylaxis and/or treatment of heart damages caused by cardiotoxic doses of drugs or chems. in large mammals and particularly humans. beings. The invention particularly relates to the prophylaxis and/or treatment of heart damages, especially myocardial damages, which may occur during cytostatic chemotherapy. The invention further relates to the utilization of these benzazepine-N-acetic acid derivs. for adjuvant treatment in therapy in which drugs, which have undesirable oxidative-toxic side effects, are used. The invention addnl. relates to the production of drugs suitable for the prophylaxis and/or treatment or adjuvant treatment. Thus, tablets were prepared from (3S,2'R)-3-(1-[2'-(ethoxycarbonyl)-4'-phenylbutyl]cyclopentane-1-carbonylamino)-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid 20, corn starch 60, lactose 135, and gelatin (10% solution) 6 mg/tablet.

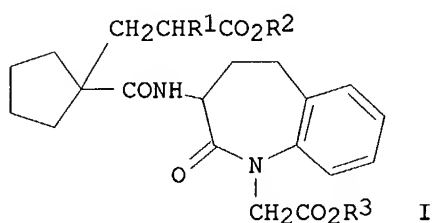
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2000:574119 CAPLUS  
DN 133:172184  
TI Medicament for treatment of high blood pressure  
IN Wilkins, Martin R.; Thormaehlen, Dirk; Waldeck, Harald  
PA Solvay Pharmaceuticals G.m.b.H., Germany  
SO Ger. Offen., 8 pp.  
CODEN: GWXXBX  
DT Patent  
LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19906310	A1	20000817	DE 1999-19906310	19990216
	WO 2000048601	A1	20000824	WO 2000-EP1068	20000210
	W: AU, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RU, SK, TR, UA, US, ZA				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	NZ 514058	A	20010928	NZ 2000-514058	20000210
	BR 2000008260	A	20011106	BR 2000-8260	20000210

EP 1154777	A1	20011121	EP 2000-903681	20000210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
TR 200102386	T2	20020121	TR 2001-200102386	20000210
JP 2002537258	T2	20021105	JP 2000-599393	20000210
ZA 2001005828	A	20020715	ZA 2001-5828	20010716
NO 2001003958	A	20011015	NO 2001-3958	20010815
US 2002052361	A1	20020502	US 2001-930186	20010816
US 6482820	B2	20021119		
PRAI DE 1999-19906310	A	19990216		
WO 2000-EP1068	W	20000210		
OS MARPAT 133:172184				
GI				

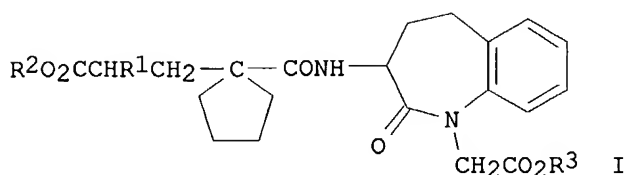


AB Benzazepine-N-acetic acid derivs. I [R1 = (substituted) phenylalkyl, naphthylalkyl; R2, R3 = H, biolabile ester-forming group] are useful for treatment of high blood pressure regardless of etiol., especially certain forms of secondary hypertension associated with noncardiac disorders. Thus, rats with hypoxia-induced pulmonary hypertension, treated with (3S,2'R)-3-[1-(2-carboxy-4-phenylbutyl)cyclopentane-1-carbonylamino]-2,3,4,5-tetrahydro-2-oxo-(1H)-1-benzazepine-1-acetic acid (II) (40 mg/kg i.p./day by osmotic minipump), showed a reduction in pulmonary arterial pressure with no effect on the systemic blood pressure. A sterile injection solution contained II 10, Na2HPO4.7H2O 43.24, NaH2PO4.2H2O 7.72, NaCl 30.0, and H2O 4948.0 mg.

L4 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN  
 AN 1998:196303 CAPLUS  
 DN 128:239479  
 TI Benzazepineacetic acid derivatives promoting gastrointestinal blood circulation  
 IN Rozsa, Susanna; Papp, Julius Gy.; Thormaehlen, Dirk; Waldeck, Harald  
 PA Solvay Pharmaceuticals G.m.b.H., Germany  
 SO Ger. Offen., 20 pp.  
 CODEN: GWXXBX  
 DT Patent  
 LA German  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	DE 19638020	A1	19980319	DE 1996-19638020	19960918
	EP 830863	A1	19980325	EP 1997-115603	19970909
	EP 830863	B1	20000510		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	ES 2145545	T3	20000701	ES 1997-115603	19970909
	US 5783573	A	19980721	US 1997-929114	19970915
	JP 10101565	A2	19980421	JP 1997-251928	19970917

PRAI DE 1996-19638020 A 19960918  
 OS MARPAT 128:239479  
 GI



AB Benzazepineacetic acid derivs. I [R1 = (substituted) phenylalkyl, naphthylalkyl; R2, R3 = H, group forming a biol. labile ester] and their salts are useful in pharmaceutical compns. for treatment and/or prophylaxis of disorders in the gastrointestinal (mesenteric) circulation of various etiol. in humans and large mammals. Thus, in rats with streptozotocin-induced diabetes, the mesenteric arterial blood pressure was 9 mL/min; this was increased to 14 mL/min by treatment with I (substituents not specified) at 30 mg/kg/day orally for 8 wk. Tablets were prepared containing (3S,2R)-I (R1 = PhCH2CH2, R2 = Et, R3 = H) (II) 20, corn starch 60, lactose 135, and gelatin 6 mg. II was prepared from di-Et malonate and phenethyl bromide via 2-carboxy-4-phenylbutyric acid and Et  $\alpha$ -(2-phenethyl)acrylate, reaction with cyclopentanecarboxylic acid, resolution with L(-)- $\alpha$ -methylbenzylamine, condensation with tert-Bu 3-amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetate, etc.

L4 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1996:646474 CAPLUS

DN 125:301029

TI Preparation of 3-[[[(1-carboxyalkyl)cyclopentyl]carbonylamino]benzazepin-1-acetates and analogs as neutral endopeptidase inhibitors

IN Waldeck, Harald; Hoeltje, Dagmar; Messinger, Josef; Antel, Jochen; Wurl, Michael; Thormaehlen, Dirk

PA Kali-Chemie Pharma GmbH, Germany

SO Eur. Pat. Appl., 35 pp.

CODEN: EPXXDW

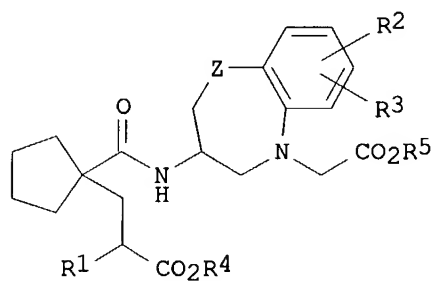
DT Patent

LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 733642	A1	19960925	EP 1996-104265	19960318
	EP 733642	B1	20001129		
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	DE 19510566	A1	19960926	DE 1995-19510566	19950323
	ZA 9601243	A	19960827	ZA 1996-1243	19960216
	IL 117265	A1	20000716	IL 1996-117265	19960226
	SK 281079	B6	20001107	SK 1996-354	19960315
	AT 197801	E	20001215	AT 1996-104265	19960318
	ES 2152444	T3	20010201	ES 1996-104265	19960318
	PT 733642	T	20010330	PT 1996-104265	19960318
	CN 1147506	A	19970416	CN 1996-104257	19960320
	CN 1059436	B	20001213		
	RU 2159768	C2	20001127	RU 1996-105383	19960320
	CA 2172354	AA	19960924	CA 1996-2172354	19960321
	CA 2172354	C	20021008		
	AU 9648210	A1	19961003	AU 1996-48210	19960321
	AU 701271	B2	19990121		
	NO 9601181	A	19960924	NO 1996-1181	19960322

JP 08269011	A2	19961015	JP 1996-66703	19960322
US 5677297	A	19971014	US 1996-620213	19960322
CZ 289245	B6	20011212	CZ 1996-863	19960322
PL 184336	B1	20021031	PL 1996-313433	19960322
GR 3035410	T3	20010531	GR 2001-400240	20010214
PRAI DE 1995-19510566	A	19950323		
OS MARPAT 125:301029				
GI				



AB Title compds. (I; R1 = alkoxyalkoxyalkyl, phenylalkyl, phenoxyalkyl, etc.; R2, R3 = H or halo; R4, R5 = H, metabolism labile ester residue; Z = CH<sub>2</sub>, O, S) were prepared. Thus, tert-Bu 3-amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetate was amidated by 1-(2-ethoxycarbonyl-4-phenylbutyl)cyclopentanecarboxylic acid (preparation each given) to give I (R1 = CH<sub>2</sub>CH<sub>2</sub>Ph, R2 = R3 = H, R4 = Et, R5 = CMe<sub>3</sub>, Z = CH<sub>2</sub>). Data for in vitro and in vivo biol. activity of I were given.

=>

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DICTIONARY FILE UPDATES: 31 MAY 2004 HIGHEST RN 688001-12-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

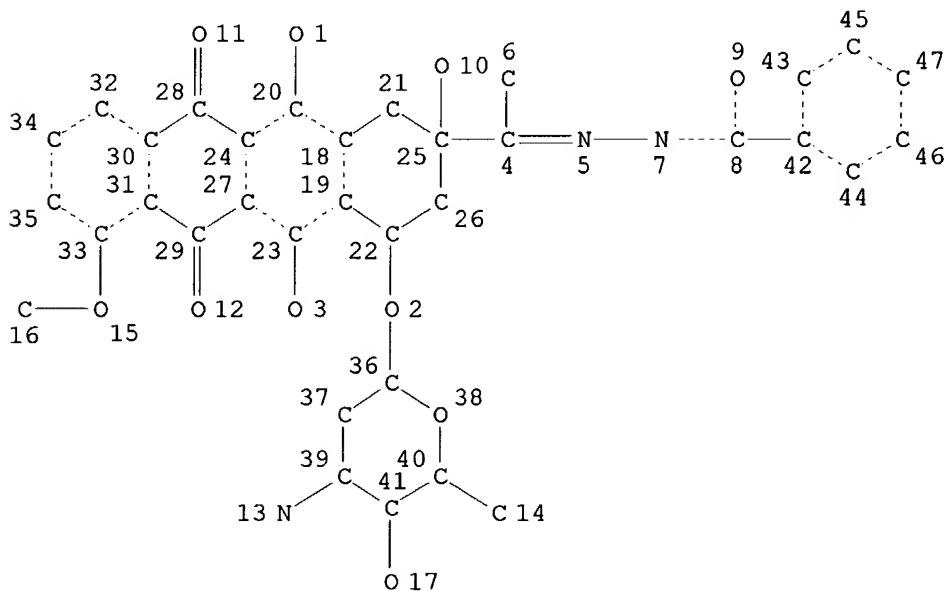
Experimental and calculated property data are now available. For more  
information enter HELP PROP at an arrow prompt in the file or refer  
to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> s zorubicin/cn  
L2 1 ZORUBICIN/CN

=> d rn

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 54083-22-6 REGISTRY

=> str 54083-22-6  
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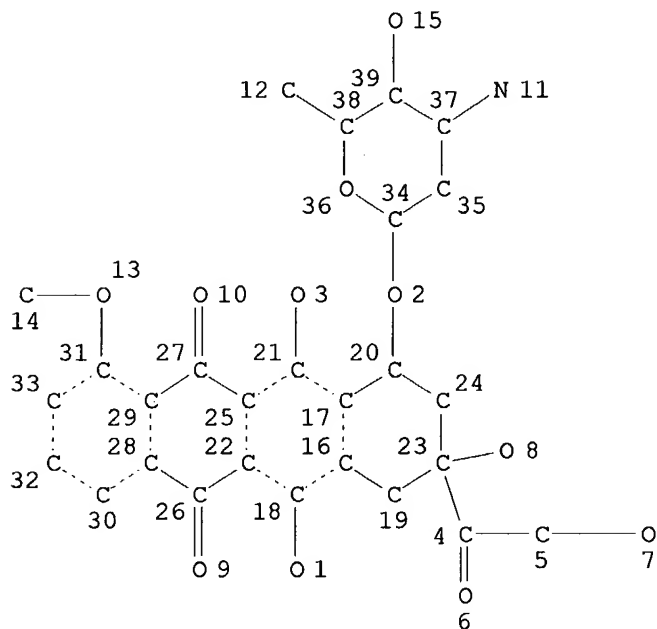
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=> s doxorubicin/cn  
L4 1 DOXORUBICIN/CN

=> d rn

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 23214-92-8 REGISTRY

=> str 23214-92-8  
WARNING. STEREO DATA NOT INCLUDED IN MODEL (NOT SEARCHABLE)  
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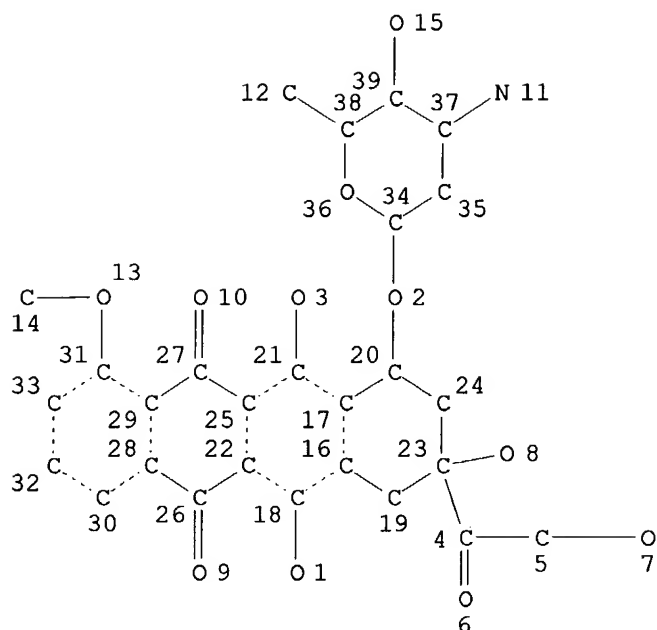
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L5 STRUCTURE CREATED

=> s epirubicin/cn  
L6 1 EPIRUBICIN/CN

=> d rn

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 56420-45-2 REGISTRY

=> str 56420-45-2  
WARNING. STEREO DATA NOT INCLUDED IN MODEL (NOT SEARCHABLE)  
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L7 STRUCTURE CREATED

=> s mitoxantrone

L8 6 MITOXANTRONE

=> d rn

L8 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 218350-47-1 REGISTRY

=> str 218350-47-1

218350-47-1 MAY NOT BE USED AS A MODEL

Structures which were created via the STRUCTURE command or are in the Fragment File may be used as models in the STRUCTURE command. Most, but not all, substance Accession Numbers can also be used.

ENTER NAME OF STRUCTURE TO BE RECALLED (NONE):none

:end

NO STRUCTURE CREATED

=> d l8 1-6 sub bib abs

L8 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 218350-47-1 REGISTRY

CN DNA (human clone MXR2 transport protein ABC (ATP-binding cassette-containing) cDNA plus flanks) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN **DNA (human S1-M1-80 cell clone MXR2 gene MXR2 mitoxantrone resistance protein 2 cDNA plus flanks)**

CN GenBank AF093772

FS NUCLEIC ACID SEQUENCE

MF Unspecified

CI MAN

SR GenBank

LC STN Files: CA, CAPLUS, GENBANK

DT.CA Caplus document type: Journal

RL.NP Roles from non-patents: BIOL (Biological study); PRP (Properties)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
\*\*\* USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE \*\*\*  
1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 130:248466 CA  
TI Molecular cloning of cDNAs which are highly overexpressed in  
mitoxantrone-resistant cells: Demonstration of homology to ABC transport  
genes  
AU Miyake, Keisuke; Mickley, Lyn; Litman, Thomas; Zhan, Zhirong; Robey,  
Robert; Cristensen, Barbara; Brangi, Mariafiorella; Greenberger, Lee;  
Dean, Michael; Fojo, Tito; Bates, Susan E.  
CS Medicine Branch National Cancer Institute, NIH, Bethesda, MD, 20892, USA  
SO Cancer Research (1999), 59(1), 8-13  
CODEN: CNREA8; ISSN: 0008-5472  
PB AACR Subscription Office  
DT Journal  
LA English  
AB Reports of multiple distinct mitoxantrone-resistant sublines without  
overexpression of P-glycoprotein or the multidrug-resistance associated  
protein have raised the possibility of the existence of another major  
transporter conferring drug resistance. In the present study, a cDNA  
library from mitoxantrone-resistant S1-M1-80 human colon carcinoma cells  
was screened by differential hybridization. Two cDNAs of different  
lengths were isolated and designated MXR1 and MXR2. Sequencing revealed a  
high degree of homol. for the cDNAs with Expressed Sequence Tag sequences  
previously identified as belonging to an ATP binding cassette transporter.  
Homol. to the Drosophila white gene and its homologues was found for the  
predicted amino acid sequence. Using either cDNA as a probe in a Northern  
anal. demonstrated high levels of expression in the S1-M1-80 cells and in  
the human breast cancer subline, MCF-7 AdVp3000. Levels were lower in  
earlier steps of selection, and in partial revertants. The gene is  
amplified 10-12-fold in the MCF-7 AdVp3000 cells, but not in the S1-M1-80  
cells. These studies are consistent with the identification of a new ATP  
binding cassette transporter, which is overexpressed in  
mitoxantrone-resistant cells.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 218350-46-0 REGISTRY  
CN DNA (human clone MXR1 transport protein ABC (ATP-binding  
cassette-containing) C-terminal fragment-specifying cDNA plus 3'-flank)  
(9CI) (CA INDEX NAME)

OTHER NAMES:

CN 2378: PN: WO03038130 FIGURE: 3 claimed DNA  
CN 3: PN: WO03008647 TABLE: 13b unclaimed DNA  
CN **DNA (human S1-M1-80 cell clone MXR1 gene MXR1 mitoxantrone resistance  
protein 1 C-terminal fragment-specifying cDNA plus 3'-flank)**  
CN GenBank AF093771  
FS NUCLEIC ACID SEQUENCE  
MF Unspecified  
CI MAN  
SR GenBank  
LC STN Files: CA, CAPLUS, GENBANK, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Journal; Patent  
RL.P Roles from patents: BIOL (Biological study); PRP (Properties)  
RL.NP Roles from non-patents: BIOL (Biological study); PRP (Properties)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
 \*\*\* USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE \*\*\*  
 4 REFERENCES IN FILE CA (1907 TO DATE)  
 4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 138:380471 CA  
 TI Genes that are differentially expressed during erythropoiesis and their  
 diagnostic and therapeutic uses  
 IN Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke,  
 Martin; Lemke, Britt; Hacker, Christine  
 PA Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin  
 SO PCT Int. Appl., 285 pp.  
 CODEN: PIXXD2

DT Patent  
 LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003038130	A2	20030508	WO 2002-US34888	20021031
	WO 2003038130	A3	20040212		
	WO 2003038130	C1	20040422		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2004014064	A1	20040122	US 2002-285366	20021031
PRAI	US 2001-335048P		20011031		
	US 2001-335183P		20011102		
	WO 2002-US34888		20021031		
AB	The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized				

genes. This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.

## REFERENCE 2

AN 138:148639 CA  
 TI Comparison of protein or gene expression patterns of blood cells obtained by microarray to injury database to assess injury  
 IN Sharp, Frank R.; Tang, Yang; Lu, Aigang  
 PA University of Cincinnati, USA  
 SO PCT Int. Appl., 126 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003008647	A2	20030130	WO 2001-US44278	20011128
	WO 2003008647	A3	20040325		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2003104393	A1	20030605	US 2001-996275	20011128
PRAI	US 2000-253568P		20001128		
AB	Methods of injury assessment in an individual include the steps of determining				
a					

pattern of expression exhibited by blood cells obtained from an individual and comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury. The injury database includes genomic injury databases, proteomic injury databases, organ specific injury database, disease specific injury database. The patterns of gene or protein expression are obtained by microarray and analyzed by statistical anal., class prediction, clustering, and computer programs. The genes in the pattern of gene expression comprise acidosis-induced genes, hypoxia-induced genes, glucose-induced genes, ischemia-induced genes. The invention relates to sequences of two human genes which are expressed more highly in Parkinson's individuals. The invention also relates to genes associated with status epilepticus, hypoglycemia, ischemic stroke and hemorrhagic stroke in rat model. The invention also relates to gene expression pattern in males and females, resp. The invention also relates to assessing Parkinson's disease, stroke profusion, drug, neurofibromatosis, manic bipolar depression, migraine headache, schizophrenia, and Tourettes disease based on pattern of expression.

## REFERENCE 3

AN 137:88421 CA  
 TI Genetic polymorphisms in genes associated with drug metabolism and their use in selecting drug therapies  
 IN Stanton, Vincent; Zillmann, Martin  
 PA USA  
 SO U.S. Pat. Appl. Publ., 210 pp., Cont.-in-part of U.S. Ser. No. 710,467.  
 CODEN: USXXCO  
 DT Patent  
 LA English

FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2001034023	A1	20011025	US 2000-733000	20001207
	WO 2000050639	A2	20000831	WO 2000-US1392	20000120
	WO 2000050639	A3	20020510		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001034023	A1	20011025	US 2000-733000	20001207
PRAI	US 1999-131334P		19990426		
	US 1999-139440P		19990615		
	WO 2000-US1392		20000120		
	US 2000-696482		20001024		
	US 2000-710467		20001108		
	US 2000-733000		20001207		
	US 1999-121047P		19990222		
	US 1999-357743		19990720		
AB	Methods for identifying and utilizing variances in genes relating to efficacy and safety of medical therapy and other aspects of medical therapy are described, including methods for selecting an effective treatment. [This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].				

#### REFERENCE 4

AN 130:248466 CA

TI Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells: Demonstration of homology to ABC transport genes

AU Miyake, Keisuke; Mickley, Lyn; Litman, Thomas; Zhan, Zhirong; Robey, Robert; Cristensen, Barbara; Brangi, Mariafiorella; Greenberger, Lee; Dean, Michael; Fojo, Tito; Bates, Susan E.

CS Medicine Branch National Cancer Institute, NIH, Bethesda, MD, 20892, USA

SO Cancer Research (1999), 59(1), 8-13

CODEN: CNREA8; ISSN: 0008-5472

PB AACR Subscription Office

DT Journal

LA English

AB Reports of multiple distinct mitoxantrone-resistant sublines without overexpression of P-glycoprotein or the multidrug-resistance associated protein have raised the possibility of the existence of another major transporter conferring drug resistance. In the present study, a cDNA library from mitoxantrone-resistant S1-M1-80 human colon carcinoma cells was screened by differential hybridization. Two cDNAs of different lengths were isolated and designated MXR1 and MXR2. Sequencing revealed a high degree of homol. for the cDNAs with Expressed Sequence Tag sequences previously identified as belonging to an ATP binding cassette transporter. Homol. to the Drosophila white gene and its homologues was found for the predicted amino acid sequence. Using either cDNA as a probe in a Northern anal. demonstrated high levels of expression in the S1-M1-80 cells and in the human breast cancer subline, MCF-7 AdVp3000. Levels were lower in earlier steps of selection, and in partial revertants. The gene is amplified 10-12-fold in the MCF-7 AdVp3000 cells, but not in the S1-M1-80 cells. These studies are consistent with the identification of a new ATP

binding cassette transporter, which is overexpressed in mitoxantrone-resistant cells.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 158439-26-0 REGISTRY

CN 9,12-Octadecadienoic acid (9Z,12Z)-, 9,10-dihydro-5-hydroxy-9,10-dioxo-1,4-anthracenediylbis(imino-2,1-ethanediylimino-2,1-ethanediyl) ester (9CI)  
(CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 9,12-Octadecadienoic acid (Z,Z)-, 9,10-dihydro-5-hydroxy-9,10-dioxo-1,4-anthracenediylbis(imino-2,1-ethanediylimino-2,1-ethanediyl) ester

OTHER NAMES:

CN **Mitoxantrone dilinoleate**

MF C58 H88 N4 O7

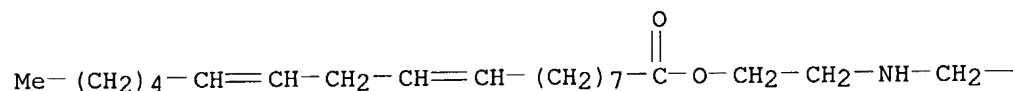
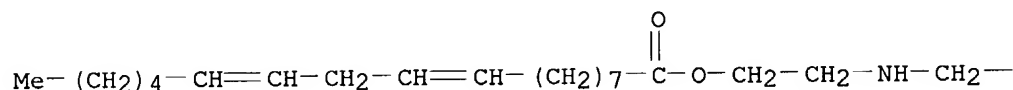
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

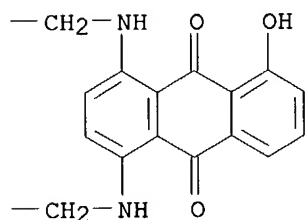
DT.CA Caplus document type: Journal

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation);  
USES (Uses)

PAGE 1-A



PAGE 1-B



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 121:238252 CA

TI Incorporation of lipophilic prodrugs of ametantrone and mitoxantrone inside low density lipoproteins (LDL) and selective uptake of the prodrug LDL complex via the LDL receptor pathway

AU Monard-Herkt, F.; Teissier-Morier, E.; Favre, G.; Samadi-Baboli, M.; Soula, G.; Houssin, R.; Bernier, J. L.; Henichart, J. P.; Martin-Nizard, F.; et al.  
 CS Pasteur Institute, Lille, Fr.  
 SO Acta Therapeutica (1993), 19(4), 317-35  
 CODEN: ACTTDZ; ISSN: 0378-0619  
 DT Journal  
 LA English  
 AB Low-d. lipoprotein (LDL) particles are potential drug carriers, but only lipophilic drug species partition into the core of the system. In this study, ametantrone (AQ) and mitoxantrone (DHAQ) have been coupled to different fatty acids (stearate, palmitate, oleate, linolenate). The linolenate esters of AQ and DHAQ incorporate in highest concentration into LDL using the following protocol of incubation. The prodrug (dilinolenate of DHAQ) was dissolved in Intralipid (a parental triglyceride rich emulsion) and then incubated with LDL and lipoprotein deficient serum or albumin for 18 h at 37°C. This method provides substantial incorporation of dilinolenate-DHAQ into LDL (26 mols. of dilinolenate-DHAQ per LDL particle). The dilinolenate-DHAQ-LDL complex was recognized by apolipoprotein B and E receptors, in vitro and in vivo in the rabbit. The pharmacol. efficiency of both free dilinolenate-DHAQ and dilinolenate-DHAQ-LDL complex was 1000 times less cytotoxic on A 549, A 431 and L 1210 cells than free DHAQ. We conclude that this method of incorporation allows the incorporation of a consistent concentration of prodrug inside LDL and prevents aggregation of the lipoprotein during the preparation of the prodrug-LDL complex. This complex is incorporated into the cell both in vitro and in vivo via the LDL receptor pathway.

L8 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
 RN 70711-41-0 REGISTRY  
 CN 9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-, diacetate (salt) (9CI) (CA INDEX NAME)

OTHER NAMES:

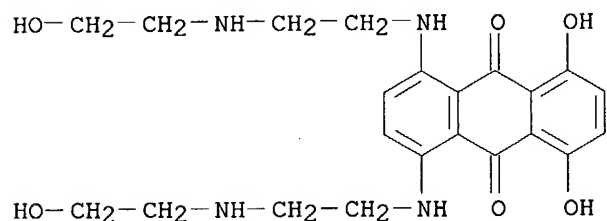
CN **Mitoxantrone diacetate**  
 CN NSC 299195  
 DR 137635-97-3  
 MF C22 H28 N4 O6 . 2 C2 H4 O2  
 LC STN Files: BIOSIS, CA, CAPLUS, IMSPATENTS, IMSRESEARCH, RTECS\*, TOXCENTER

(\*File contains numerically searchable property data)

DT.CA Caplus document type: Journal; Patent  
 RL.P Roles from patents: PREP (Preparation)  
 RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

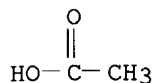
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 CMF C22 H28 N4 O6



CM 2

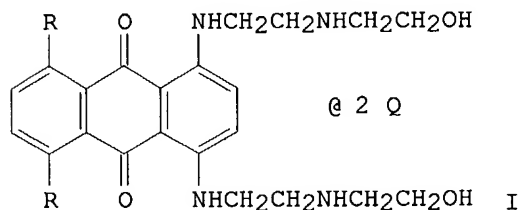
CRN 64-19-7  
CMF C2 H4 O2



8 REFERENCES IN FILE CA (1907 TO DATE)  
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 119:116918 CA  
TI Synthesis and characterization of anticancer anthraquinones: ametantrone and mitoxantrone  
AU Chang, Pong  
CS Sch. Pharm., Natl. Def. Med. Cent., Taipei, Taiwan  
SO Proceedings of the National Science Council, Republic of China, Part A: Physical Science and Engineering (1992), 16(4), 304-10  
CODEN: PNAEE2; ISSN: 0255-6588  
DT Journal  
LA English  
GI



AB Ametantrone (I, R = H, Q = AcOH) (3) and mitoxantrone I (R = OH, Q = HCl) are anthraquinone derivs. which possess potent cytotoxic activity against a variety of cancers in both animal and clin. studies. Ametantrone 3 was prepared by reacting leucoquinizarin 1 with 2-(2-aminoethylamino)ethanol, followed by air oxidation. The corresponding leuco-compound, 2,3-dihydro-1,4,5,8-tetrahydroxy-9,10-anthracenedione 7, for the synthesis of mitoxantrone was not available. A synthetic route starting from chrysazin (4) was thus developed. Nitration of chrysazin 4, followed by reduction of the nitro-product gave 1,8-dihydroxy-4,5-diaminoanthraquinone (6), which on reductive hydrolysis yields 7. Then, by using the same procedures and reaction conditions as in the synthesis of ametantrone, mitoxantrone could be prepared with a total yield of 32%. Antileukemic activity of the synthesized mitoxantrone was conducted and proved to be equally potent by comparing with a com. product.

REFERENCE 2

AN 116:20794 CA  
TI Preparation of 1,4-bis[(alkylamino)alkylamino]-9,10-anthracenediones  
IN Zoelch, Lothar; Loeffler, Ralph; Kochmann, Werner; Holtz, Helmar; Schwabe, Konrad; Redslob, Joachim; Niclas, Hans Joachim; Heyer, Thomas; Buttke,

Klaus; et al.

PA Arzneimittelwerk Dresden G.m.b.H., Germany

SO Ger. (East), 6 pp.

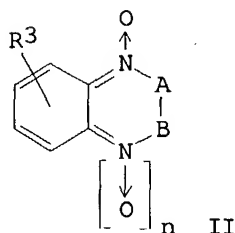
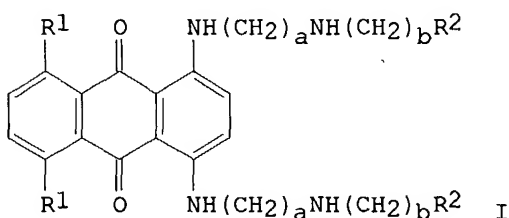
CODEN: GEXXA8

DT Patent

LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DD 290774	A7	19910613	DD 1988-312356	19880121
PRAI	DD 1988-312356		19880121		
GI					



AB Title compds. I ( $R_1, R_2 = H, OH, NH_2$ ;  $a, b = 2-4$ ;  $R_1, R_2, a, b$  can be the same or different) were prepared via oxidation of the corresponding 2,3-dihydro derivs. by 1-2 equivalent amine oxide II ( $R_3 = H, Me, MeO, halo, NO_2$ ;  $AB = O, R_4C:CR_5$ ;  $R_4, R_5 = H, Me$ ;  $n = 0, 1$ ;  $n = 0$  when  $AB = O$ ) at  $10-30^\circ$  in an organic solvent, e.g., ethylene glycol monomethyl ether optionally in the presence of an organic or inorg. acid. Thus, 5-methoxybenzofuroxan was added to a solution of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxy-2,3-dihydro-9,10-anthracenedione in  $MeOCH_2OH$  at  $0^\circ$ . After 30 min at  $0^\circ$ , ethanolic HCl was added and the mixture was stirred 15 min further at  $0^\circ$ , ethanolic HCl was added and the mixture was stirred 15 min further at  $0^\circ$ , then warmed to  $23^\circ$ . The solution was stirred 20h at  $23^\circ$  to give the oxidized product in 91.1% yield.

#### REFERENCE 3

AN 113:184681 CA  
TI Evidence for a common mechanism of action for antitumor and antibacterial agents that inhibit type II DNA topoisomerases  
AU Huff, Anne C.; Kreuzer, Kenneth N.  
CS Med. Cent., Duke Univ., Durham, NC, 27710, USA  
SO Journal of Biological Chemistry (1990), 265(33), 20496-505  
CODEN: JBCHA3; ISSN: 0021-9258  
DT Journal  
LA English  
AB Numerous antitumor and antibacterial agents inhibit type II DNA topoisomerases, yielding, in each case, a complex of enzyme covalently bound to cleaved DNA. The mechanism of inhibitor action was investigated by using the type II DNA topoisomerase of bacteriophage T4 as a model. The T4 topoisomerase is the target of antitumor agent 4'-(9-acridinylamino)methanesulfon-4-anisidide (m-AMSA) in T4-infected Escherichia coli. Two m-AMSA-resistant phage strains were previously isolated, one with a point mutation in topoisomerase subunit gene 39 and the other with a point mutation in topoisomerase subunit gene 52. The present study shows that the wild-type T4 topoisomerase is inhibited by six addnl. antitumor agents that also inhibit the mammalian type II topoisomerase: elipticine, 9-hydroxyellipticine, 2-methyl-9-hydroxyellipticinium acetate, mitoxantrone diacetate, teniposide, and

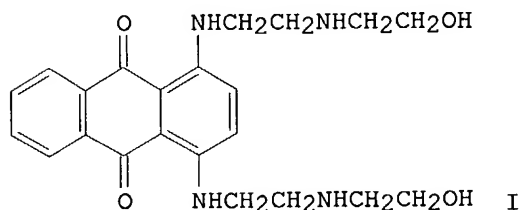
etoposide. Further, one or both of the m-AMSA-resistance mutations alters the enzyme sensitivity to each of these agents, conferring either cross-resistance or enhanced sensitivity. Finally, the gene 39 mutation confers on T4 topoisomerase a DNA gyrase-like sensitivity to the gyrase inhibitor oxolinic acid, thus establishing a direct link between the mechanism of action of the antibacterial quinolones and that of the antitumor agents. These results strongly suggest that diverse inhibitors of type II topoisomerases share a common binding site and a common mechanism of action, both of which are apparently conserved in the evolution of the type II DNA topoisomerases. Alterations in DNA cleavage site specificity caused by either the inhibitors or the m-AMSA-resistance mutations favor the proposal that the inhibitor binding site is composed of both protein and DNA.

#### REFERENCE 4

AN 111:70338 CA  
 TI Inhibitory effects of mitoxantrone and its analogs on a human hepatoma cell line in vitro  
 AU Liu, Tsung Yun; Yeh, Chang Huei; Chi, Chin Wen  
 CS Dep. Med. Res., Veterans Gen. Hosp., Taipei, Taiwan  
 SO Medical Science Research (1989), 17(12), 529-30  
 CODEN: MSCREJ; ISSN: 0269-8951  
 DT Journal  
 LA English  
 AB Among 4 anthracenediones tested, mitoxantrone (NSC 301739) was most potent against human hepatoma cells in vitro. Mitoxantrone, which is a HCl salt, was more active than the free base (NSC 279836), the diacetate (NSC 299195), and anthracenedione (NSC 196473). Mitoxantrone was cytotoxic compared to adriamycin in this system.

#### REFERENCE 5

AN 99:16204 CA  
 TI Comparative cytotoxicity of bisantrene, mitoxanthrone, ametantrone, dihydroxyanthracenedione, dihydroxyanthracenedione diacetate, and doxorubicin on human cells in vitro  
 AU Drewinko, Benjamin; Yang, Li Ying; Barlogie, Barthel; Trujillo, Jose M.  
 CS Dep. Lab. Med., Univ. Texas, Houston, TX, 77030, USA  
 SO Cancer Research (1983), 43(6), 2648-53  
 CODEN: CNREA8; ISSN: 0008-5472  
 DT Journal  
 LA English  
 GI

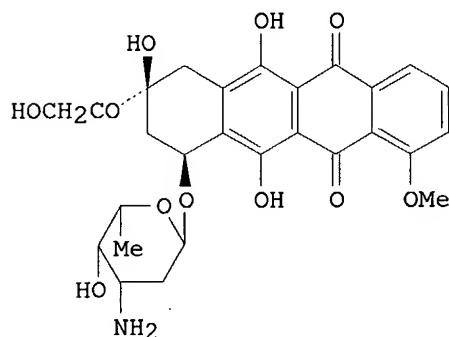


AB The cytotoxic efficacies of several substituted anthraquinones, ametantrone (I) [64862-96-0], dihydroxyanthracenedione [65271-80-9], dihydroxyanthracenedione diacetate [70711-41-0], mitoxanthrone [65271-80-9], bisantrene [78186-34-2], and doxorubicin, were evaluated on an established human colon adenocarcinoma cell line by the method of inhibition of colony formation. The concentration-dependent survival curve

following treatment for 1 h was biphasic and exponential for all agents. At concns.  $<1 \mu\text{g/mL}$ , mitoxanthrone was about twice as active as both hydroxyl-substituted anthracenediones and doxorubicin, .apprx.14 times more efficacious than I, and .apprx.22 times more powerful than bisantrene. At higher concns., these differences in efficacy became even more pronounced. Treatment in stationary phase decreased the lethal efficacy of doxorubicin but not that of the other agents. No recovery of potentially lethal or sublethal damage was noted for any agent, but for anthracenedione derivs., there was a small but statistically significant increase in cell kill during fractionated exposure. Continuous treatment with mitoxanthrone or bisantrene resulted in marked degrees of cell killing, reaching 99.95 and 99.5%, resp., after 24 h. For doxorubicin, cell kill efficacy declined after 4 h. Mitoxanthrone was 10-fold more active on cells in G2 phase than on those in mid- to late-S phase. Sensitivity in G1 phase was immediate. Thus, mitoxanthrone appears as the most active compound while bisantrene and I are the least active agents. The cytotoxic efficacy of bisantrene increases during prolonged continuous exposure, while that of mitoxanthrone increases in fractionated administration. These characteristics could be exploited in clin. strategies designed to improve the performance of these agents.

#### REFERENCE 6

AN 96:97147 CA  
 TI Inhibition of cardiac guanylate cyclase by doxorubicin and some of its analogs: possible relationship to cardiotoxicity  
 AU Lehotay, Denis C.; Levey, Barbara A.; Rogerson, Brian J.; Levey, Gerald S.  
 CS Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15261, USA  
 SO Cancer Treatment Reports (1982), 66(2), 311-16  
 CODEN: CTRRDO; ISSN: 0361-5960  
 DT Journal  
 LA English  
 GI



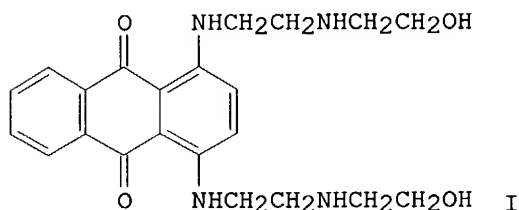
I

AB The effect of 30 analogs of doxorubicin (I) on cardiac guanylate cyclase [9054-75-5] activity. Structural modifications of these anthracycline antibiotics altered their effect on rat cardiac guanylate cyclase activity. N-Substitution on the sugar moiety eliminated the inhibitory action observed with the parent compound. Long-chain hydrocarbon substitutions in place of the Me ketone side chain had a similar effect. Removal of substitution of the C-4 methoxy group had little or no effect on the ability of these compds. to modify guanylate cyclase activity. Substitutions of the C-9 side chain by a hydrazone derivative resulted in compds. that stimulated the enzyme. All of the anthracenedione derivs. were inhibitory. A comparison of the inhibitory effect of some of these anthracycline derivs. on in vitro cardiac guanylate cyclase activity with

their cardiotoxic potency suggests a possible relationship between these 2 parameters.

#### REFERENCE 7

AN 94:132036 CA  
TI Comparative structure-genotoxicity study of three aminoanthraquinone drugs and doxorubicin  
AU Au, William W.; Butler, Mary Ann; Matney, Thomas S.; Loo, Ti Li  
CS Health Sci. Cent., Univ. Texas, Houston, TX, 77030, USA  
SO Cancer Research (1981), 41(2), 376-9  
CODEN: CNREA8; ISSN: 0008-5472  
DT Journal  
LA English  
GI

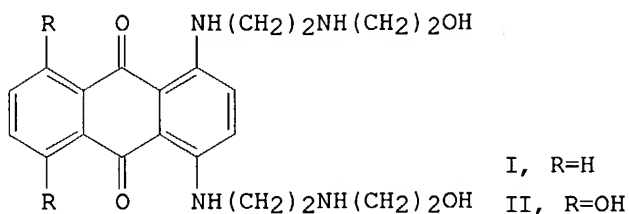


AB The genotoxic effects of 1,4-bis[2-[(2-hydroxyethyl)amino]ethylamino]-9,10-anthracenedione (HAQ) [64862-96-0] and 1,4-dihydroxy-5,8-bis[2-[(2-hydroxyethyl)amino]ethylamino]-9,10-anthracenedione (DHAQ) (I) [65271-80-9] and a new analog, 1,4-dihydroxy-5,8-bis[2-[(2-hydroxyethyl)amino]ethylamino]-9,10-anthracenedione diacetate (I diacetate) [70711-41-0], were analyzed by using mammalian cell cytogenetic assays (chromosome breakage and sister chromatid exchanges) as well as bacterial mutagenesis assays. The exptl. therapeutic activities of these drugs in vivo correlated well with their in vitro genetic toxicities as revealed by cytogenetic assays; i.e., the drug with the highest therapeutic activity (DHAQ) was most active in inducing chromosome damage. DHAQ was also more genotoxic than adriamycin [23214-92-8]. In cytogenetic assays, the activities of all drugs were reduced to different degrees in the presence of a S-9 metabolic system. Discrepancies were observed between results obtained from cytogenetic assays and those from mutagenesis assays. Whereas DHAQ was most active in cytogenetic studies, adriamycin was most mutagenic or toxic. HAQ was least active cytogenetically, and this activity was not changed appreciably in the presence of metabolic enzymes. However, it was metabolically activated to a bacterial mutagen. Apparently, the cytogenetic and mutagenesis assays may be sensitive to the activities of different agents and of different moieties of the same agent. The application of short-term in vitro assays to identify the chemical structures responsible for genetic toxicity and for therapeutic activities in vivo may lead to the better understanding of drug activities and to the development of more effective drugs.

#### REFERENCE 8

AN 91:32660 CA  
TI Experimental antitumor activity of aminoanthraquinones  
AU Johnson, Randall K.; Zee-Cheng, Robert K. Y.; Lee, William W.; Acton, Edward M.; Henry, David W.; Cheng, C. C.  
CS Life Sci. Div., Arthur D. Little, Inc., Cambridge, MA, 02140, USA  
SO Cancer Treatment Reports (1979), 63(3), 425-39  
CODEN: CTRRDO; ISSN: 0361-5960

DT Journal  
LA English  
GI



AB The activity of a number of substituted alkylaminoanthraquinones was compared in transplanted murine tumor systems including P388 and L1210 leukemias, B16 melanoma, and colon carcinoma 26. Structure-activity relations among this class of compds. are discussed. Several derivs. had very high antitumor activity in several tumor systems. Two of the most active derivs., 1,4-bis{2-[(2-hydroxyethyl)amino]ethylamino}-9,10-anthracenedione (I) [64862-96-0] and 1,4-dihydroxy-5,8-bis{2-[(2-hydroxyethyl)amino]ethylamino}-9,10-anthracenedione (II) [65271-80-9], which had curative activity in the above-mentioned tumors, were compared in considerable detail. II showed distinct advantages over I in several tumor systems and was 10-fold more potent with respect to ED range. This last difference is important for 2 reasons. First, these aminoanthraquinones are strong and persistent blue dyes and the administration of lower doses would minimize a potential cosmetic drawback of these compds. Second and most important, i.v. administration of dose levels of I which are within the therapeutic dose range on intermittent dose schedules produced convulsions and immediate death. I.v. administration of II also caused acute toxicity, but, because of its increase potency relative to antitumor activity and delayed toxicity, this acute toxicity was apparent only at doses well above the therapeutic dose range. All of the aminoanthraquinones evaluated, regardless of their activity as antitumor agents in vivo, proved to be potent inhibitors of DNA and RNA synthesis in vitro and bound strongly to DNA as evidenced by  $\Delta T_m$  values ( $\Delta T_m$  = upward shift in DNA melting temperature). Thus, the strong antitumor activity of aminoanthraquinones would appear to be due to some mechanism other than, or in addition to, DNA binding and inhibition of nucleic acid synthesis.

L8 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 70476-82-3 REGISTRY  
CN 9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-, dihydrochloride (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN Bisantrone  
CN CL 232315  
CN DHAD  
CN Immunex  
CN **Mitoxantrone dihydrochloride**  
CN **Mitoxantrone hydrochloride**  
CN Novantrone  
CN Novatrone  
CN NSC 301739  
MF C22 H28 N4 O6 . 2 Cl H  
CI COM  
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, HSDB\*, IMSCOSEARCH, IMSPATENTS, IMSRESEARCH,

IPA, MRCK\*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS, RTECS\*, SYNTHLINE,  
TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Conference; Journal; Patent

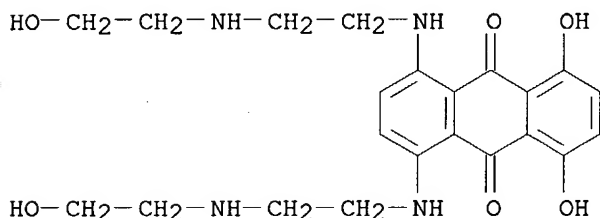
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);  
PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES  
(Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological  
study); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP  
(Properties); RACT (Reactant or reagent); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological  
study); FORM (Formation, nonpreparative)

CRN (65271-80-9)



●2 HCl

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

172 REFERENCES IN FILE CA (1907 TO DATE)

4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

172 REFERENCES IN FILE CAPLUS (1907 TO DATE)

#### REFERENCE 1

AN 140:332048 CA

TI Adjuvant cytotoxic and endocrine therapy in pre- and postmenopausal  
patients with breast cancer and one to nine infiltrated nodes. Five-year  
results of the Hellenic Cooperative Oncology Group randomized HE 10/92  
study

AU Fountzilas, George; Stathopoulos, G.; Kouvatses, G.; Polychronis, A.;  
Klouvas, G.; Samantas, E.; Zamboglou, N.; Kyriakou, K.; Adamou, A.;  
Pectasidis, D.; Ekonomopoulos, Th.; Kalofonos, H. P.; Bafaloukos, D.;  
Georgoulis, V.; Razis, E.; Koukouras, D.; Zombolas, V.; Kosmidis, P.;  
Skarlos, D.; Pavlidis, N.

CS AHEPA Hospital, Aristotle University of Thessaloniki School of Medicine,  
Thessaloniki, Greece

SO American Journal of Clinical Oncology (2004), 27(1), 57-67  
CODEN: AJCODI; ISSN: 0277-3732

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB The present randomized phase III trial was designed to detect a 15%  
benefit in relapse-free survival (RFS) or overall survival (OS) from the  
incorporation of adjuvant tamoxifen to the combination of CNF

[cyclophosphamide, 500 mg/m<sup>2</sup>; mitoxantrone (Novantrone), 10 mg/m<sup>2</sup>; fluorouracil, 500 mg/m<sup>2</sup>] chemotherapy and ovarian ablation in premenopausal patients with node-pos. breast cancer and conversely from the incorporation of CNF chemotherapy to adjuvant tamoxifen in node-pos. postmenopausal patients. From Apr. 1992 until Mar. 1998, 456 patients with operable breast cancer and one to nine infiltrated axillary nodes entered the study. Premenopausal patients were treated with six cycles of CNF chemotherapy followed by ovarian ablation with monthly injections of triptoreline 3.75 mg for 1 yr (Group A, 84 patients) or the same treatment followed by 5 yr of tamoxifen (Group B, 92 patients). Postmenopausal patients received 5 yr of tamoxifen (Group C, 145 patients) or 6 cycles of CNF followed by 5 yr of tamoxifen (Group D, 135 patients). Adjuvant radiation was administered to all patients with partial mastectomy. After a median follow-up period of 5 yr, 125 patients (27%) relapsed and 79 (17%) died. The 5-yr actuarial RFS for premenopausal patients was 65% in Group A and 68% in Group B ( $p = 0.86$ ) and for postmenopausal patients 70% in Group C and 67% in Group D ( $p = 0.36$ ). Also, the resp. OS rates were 77% and 80% ( $p = 0.68$ ) for premenopausal and 84% and 78% ( $p = 0.10$ ) for postmenopausal patients. Severe toxicities were infrequently seen, with the exception of leukopenia (18%), among the 311 patients treated with CNF. In conclusion, the present study failed to demonstrate a 15% difference in RFS in favor of node-pos. premenopausal patients treated with an addnl. 5 yr of tamoxifen after CNF adjuvant chemotherapy and ovarian ablation. Similarly, six cycles of CNF preceding 5 yr of tamoxifen did not translate to a 15% RFS benefit in node-pos. postmenopausal patients.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 2

AN 140:209872 CA  
 TI Improved liquid chromatographic method for mitoxantrone quantification in mouse plasma and tissues to study the pharmacokinetics of a liposome entrapped mitoxantrone formulation  
 AU Johnson, Jenifer L.; Ahmad, Ateeq; Khan, Sumsullah; Wang, Yue-Fen; Abu-Qare, Aqel W.; Ayoub, Jennifer E.; Zhang, Allen; Ahmad, Imran  
 CS Research and Development, Pharmacokinetics, Safety, and Efficacy Department, NeoPharm Inc., Waukegan, IL, 60085, USA  
 SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2004), 799(1), 149-155  
 CODEN: JCBAAI; ISSN: 1570-0232  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 AB A simple, rapid HPLC method for quantification of mitoxantrone in mouse plasma and tissue homogenates in the presence of a liposome entrapped mitoxantrone formulation (LEM-ETU) is described. Sample preparation is achieved by protein precipitation of 100  $\mu$ l plasma or 200  $\mu$ l tissue homogenate with an equal volume of methanol containing 0.5 M hydrochloric acid:acetonitrile (90:10, volume/volume). Ametantrone is used as the internal standard (i.s.). Mitoxantrone and i.s. are separated on a C18 reversed phase HPLC column, and quantified by their absorbance at 655 nm. In plasma, the standard curve is linear from 5 to 1000 ng/mL, and the precision (%CV) and accuracy (percentage of nominal concentration) are within 10%. In mouse tissue (heart, kidney, liver, lung, and spleen) homogenates (5%, w/v), the standard curve is linear from 25 to 2000 ng/mL, with acceptable precision and accuracy. The method was used to successfully quantify mitoxantrone in mouse plasma and tissue samples to support a pharmacokinetic study of LEM-ETU in mice.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

# REFERENCE 3

AN 140:156561 CA  
 TI Mitoxantrone (Novantrone) in multiple sclerosis: new insights  
 AU Neuhaus, Oliver; Kieseier, Bernd C.; Hartung, Hans-Peter  
 CS Department of Neurology, Heinrich Heine University, Duesseldorf, D 40225, Germany  
 SO Expert Review of Neurotherapeutics (2004), 4(1), 17-26  
 CODEN: ERNXAR; ISSN: 1473-7175  
 PB Future Drugs Ltd.  
 DT Journal; General Review  
 LA English  
 AB A review. The conclusions of a recent study of mitoxantrone (Novantrone) in multiple sclerosis and the approval of several health authorities support its use in patients with active relapsing-remitting or secondary progressive multiple sclerosis. This drug profile provides an outline on relevant preclin. and clin. studies, discusses relevant side effects of the compound and places mitoxantrone in the context of other therapeutic approaches available against this disabling disorder.  
 RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

# REFERENCE 4

AN 140:122184 CA  
 TI Clinical effects of combination therapy with mitoxantrone, vincristine, and prednisolone in breast cancer  
 AU Katsumata, Kenji; Tomioka, Hidenori; Kusama, Mikihiro; Aoki, Tatsuya; Koyanagi, Yasuhisa  
 CS Department of Surgery, Tokyo Medical University, Shinjuku-ku, Tokyo, 160-0023, Japan  
 SO Cancer Chemotherapy and Pharmacology (2003), 52(1), 86-88  
 CODEN: CCPHDZ; ISSN: 0344-5704  
 PB Springer-Verlag  
 DT Journal  
 LA English  
 AB Purpose. We assessed the clin. efficacy and safety of mitoxantrone hydrochloride which has been used as an anticancer drug in our hospital to treat breast cancer patients since 1993. Methods: A group of 23 patients with breast cancer were given one course of the following regimen every 3 wk: mitoxantrone hydrochloride (8 mg/m<sup>2</sup> i.v. day 1), vincristine sulfate (1.2 mg/m<sup>2</sup> i.v. day 1), and prednisolone (30 mg orally days 1-7). Results. The response rate was 52.2% including a complete response in four patients, and a partial response in eight patients. Adverse drug reactions included leukocytopenia (78.3%, 18/23 patients), alopecia (30.8%, 7/23), and peripheral neuropathy and generalized fatigue (26.1%, 6/23). In patients responding to the drug regimen, 50% survival was 29 mo, and in those not responding it was 12 mo. Conclusion: Combination treatment with mitoxantrone hydrochloride, vincristine sulfate and prednisolone is an effective treatment for breast cancer.  
 RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

# REFERENCE 5

AN 140:84337 CA  
 TI Field enhancement near the annealed nanostructured gold detected by optical spectroscopy with the probe biomolecules  
 AU Strekal, N.; Askirka, V.; Maskevich, S.; Sveklo, I.; Nabiev, I.  
 CS Grodno State University, Grodno, 230023, Belarus  
 SO Physics, Chemistry and Application of Nanostructures: Reviews and Short

Notes to Nanomeeting 2003, [International Conference], Minsk, Belarus, May 20-23, 2003 (2003), 171-174. Editor(s): Borisenko, Victor E.; Gaponenko, S. V.; Gurin, V. S. Publisher: World Scientific Publishing Co. Pte. Ltd., Singapore, Singapore.

CODEN: 69EJNT; ISBN: 981-238-381-6

DT Conference

LA English

AB Tailoring of spectral properties of vacuum deposited gold films with substrate annealing procedure allows to excite selectively the surface-enhanced Raman scattering (SERS) or the surface-enhanced fluorescence (SEF) of biomols. without changing a light source. The phenomenon can be explained in the context of self-assembling of gold granules on sprayed film and tuning up the position of localized plasmon (LP) excitation band to the mol. absorption. The separation of mols. from nanostructured gold surface on long distances results in further increasing of surface-enhanced secondary emission. The long-range field enhancement is discussed as collective effect of several interacting gold islands. The possible geometry of probe disposition in "hot spots" on self-aggregated gold films is presented.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 6

AN 140:64847 CA

TI Permeation of cytotoxic formulations through swatches from selected medical gloves

AU Klein, Michael; Lambov, Nikolai; Samev, Nikola; Carstens, Gerhard

CS St. Bernward-Apotheke, Hannover, Germany

SO American Journal of Health-System Pharmacy (2003), 60(10), 1006-1011

CODEN: AHSPEK; ISSN: 1079-2082

PB American Society of Health-System Pharmacists

DT Journal

LA English

AB The permeability of selected medical glove materials to various cytotoxic agents is described. Fifteen cytotoxic agents were prepared at the highest concns. normally encountered by hospital personnel. Four single-layer and two double-layer glove systems made of two materials-latex and neoprene-were exposed to the drugs for 30, 60, 90, 120, 150, and 180 min. Circular sections of the glove material were cut from the cuff and evaluated without any pretreatment. Permeability tests were conducted in an apparatus consisting of a donor chamber containing the cytotoxic solution and a collection chamber filled with water (the acceptor medium). The two sections were separated by the glove material. Permeating portions, collected in water as the acceptor medium, were analyzed by either UV-visible light spectrophotometry or high-performance liquid chromatog. (HPLC). Permeation rates were calculated on the basis of the concentration of the cytotoxic agent in the acceptor medium. Spectrophotometric measurements were taken every 30 min, and HPLC anal. was performed at the end of the three-hour period. Average permeation rates for 14 drugs were low ( $<0.2$  nmol/[min  $\cdot$  cm<sup>2</sup>]) or no permeation was detected in all glove materials. All glove materials tested were impermeable to most of the cytotoxic agents over a period of three hours. Carmustine was the only agent that substantially permeated single-layer latex glove materials. Permeation of most tested cytotoxic formulations was low through swatches of material from various medical gloves.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 7

AN 140:35511 CA  
 TI First-line intra-arterial chemotherapy (IAC) with epirubicin and mitoxantrone in locally advanced breast cancer  
 AU Fiorentini, G.; Tsetis, D.; Bernardeschi, P.; Varveris, C.; Rossi, S.; Kalogeraki, A.; Athanasakis, E.; Dentico, P.; Kanellos, P.; Biancalani, M.; Alamarashdah, S.; Zacharioudakis, G.; Saridaki, Z.; Chalkiadakis, G.; Xynos, E.; Zoras, O.  
 CS Department of Oncology and Hematology, "S. Giuseppe" City Hospital, Florence, Italy  
 SO Anticancer Research (2003), 23(5B), 4339-4345  
 CODEN: ANTRD4; ISSN: 0250-7005  
 PB International Institute of Anticancer Research  
 DT Journal  
 LA English  
 AB Approx. 20% of patients with breast cancer present with locally advanced disease without distant metastases. This phase II double-center trial aimed at investigating the activity of epirubicin (Farmorubicin) - mitoxantrone (Onkotrone/Novantrone) combination as first-line intra-arterial chemotherapy (IAC) in locally advanced breast cancer patients. Thirty-six patients with locally advanced disease and no prior exposure to anthracyclines received the following regimen: epirubicin (Farmorubicin) 30 mg/mq and mitoxantrone (Onkotrone/Novantrone) 10 mg/mq by IAC short infusion on day 1, every 3 wk for up to six cycles. Prior to IAC an arteriogram of subclavian, internal mammary and lateral thoracic arteries was obtained in all patients, followed by infusion of a blue dye solution into the arteries to determine the most appropriate vessel that supplies the tumor area. Objective responses, confirmed at least 4 wk after the first documentation, were observed in 25 patients (70%; 95%CI, 62% to 80%): 3 CR, 22 PR. Although three of the patients showed complete tumor regression, operative removal or toilet mastectomy became feasible in 25 patients since tumor shrinkage ranged over 75%. A total of 25 mastectomies were carried out for 36 patients. Four patients had bulky tumors (>13 cm tumor diameter), while 8 patients had ulcerated tumors, two of which presented with complete infiltration of normal breast tissue. The median time to progression and median overall survival were 11 and 27 mo, resp. The time to local response was 3 wk and time to mastectomy was 9 wk. Transient neurol. disorders developed in six patients and skin chemical burns with painful inflammatory reactions were encountered in ten patients. No systemic toxicity was observed in terms of bone marrow depression and hair loss. No cardiotoxicity was observed. In all specimens necrosis was reported (complete 3 cases, partial 16 and minimal 6). A combination of epirubicin (Farmorubicin) and mitoxantrone (Onkotrone/Novantrone) as IAC appears to be a safe and well tolerated treatment for locally advanced breast cancer without clin. evidence of distant metastases. When combined with surgery it offers interesting results in terms of local control and allows a high rate of mastectomies in otherwise inoperable cases.  
 RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 8

AN 140:19910 CA  
 TI Pharmaceutical compositions for coating medical implants  
 IN Hunter, William L.; Gravett, David M.; Toleikis, Philip M.; Liggins, Richard T.; Loss, Troy A. E.  
 PA Angiotech Pharmaceuticals, Inc., Can.  
 SO PCT Int. Appl., 169 pp.  
 CODEN: PIXXD2  
 DT Patent

LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003099346	A2	20031204	WO 2003-US16719	20030527
	WO 2003099346	A3	20040318		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2004043052	A1	20040304	US 2003-447309	20030527

PRAI US 2002-383419P 20020524

AB Medical implants are provided which release an anthracycline, fluoropyrimidine, folic acid antagonist, podophyllotoxin, camptothecin, hydroxyurea, and/or platinum complex, thereby inhibiting or reducing the incidence of infection associated with the implant. Thus, a solution was prepared by dissolving 100-mg 5-FU into 20-mL MeOH. A polyurethane catheter tubing was immersed in this solution for 16 h. The catheter tubing was vacuum dried at 50° for 16 h.

#### REFERENCE 9

AN 140:12588 CA  
TI Reversal of multidrug resistance in mouse lymphoma cells by phenothiazines  
AU Molnar, Joseph; Molnar, Annamaria; Mucsi, Ilona; Pinter, Oliver; Nagy, Beatrix; Varga, Andreas; Motohashi, Noboru  
CS Department of Microbiology, Albert Szent-Gyorgyi Medical University, Szeged, Hung.  
SO In Vivo (2003), 17(2), 145-150  
CODEN: IVIVE4; ISSN: 0258-851X  
PB International Institute of Anticancer Research  
DT Journal  
LA English  
AB Various compds. were tested with regard to their reversal of multidrug resistance (MDR) in mouse tumor cells transfected with the human MDR1 gene. Phenothiazines containing aromatic moieties were bound through stacking interaction involving the polarization of the aromatic amino-acid substituents at the target site of p-glycoprotein (Pgp) 170, as a consequence of their large dipoles (as in the binding of phenothiazine to calmodulin-like structures). Acting as a calcium channel blocker, verapamil may induce conformational changes in the calcium channel-like structures of the transmembrane regions of Pgp. Most probably the tyrosine moieties of Pgp are involved in the action of verapamil and phenothiazines. Tomato lectin specifically binds to the polylactosamine moiety of Pgp170 at the first loop of Pgp. Other targets in the membrane may exist in close proximity to Pgp170, such as conA-reactive glycoproteins with terminal mannosyl residues. WGA-reactive N-acetyl glucosamine residues can also be modified resulting in conformational changes in transmembrane regions of the ABC transporter. The authors' results demonstrate that MDR can be reversed by interaction of various compds. with Pgp or by modification of the membrane structure around the Pgp.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

# REFERENCE 10

AN 140:619 CA  
 TI Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. [Erratum to document cited in CA138:379010]  
 AU Ghalie, R. G.; Edan, G.; Laurent, M.; Macuch, E.; Eisenman, S.; Hartung, H. P.; Gonsette, R. E.; Butine, M. D.; Goodkin, D. E.  
 CS Immunex Corp., Seattle, WA, USA  
 SO Neurology (2003), 60(1), 157  
 CODEN: NEURAI; ISSN: 0028-3878  
 PB Lippincott Williams & Wilkins  
 DT Journal  
 LA English  
 AB There is an error in the dosage listed on page 910, under the Results section. The beginning of the second paragraph of the Results section should read as follows: "Phase 3 trial of MITO in MS (MIMS trial). Of the 124 patients who received MITO in the MIMS trial, 64 received 5 mg/m2 MITO and 60 received 12 mg/m2 MITO every 3rd month for up to 2 yr.".

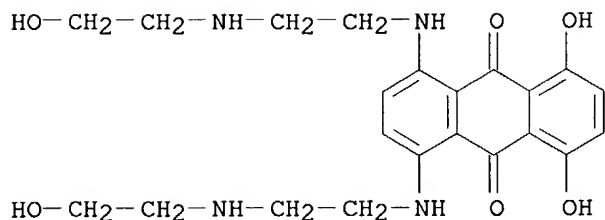
L8 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
 RN 65271-80-9 REGISTRY  
 CN 9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]- (9CI) (CA INDEX NAME)

OTHER NAMES:  
 CN 1,4-Bis[(2-(2-hydroxyethylamino)ethyl)amino]-5,8-dihydroxyanthraquinone  
 CN 1,4-Dihydroxy-5,8-bis-[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthraquinone  
 CN 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione  
 CN DHAQ  
 CN Dihydroxyanthraquinone  
 CN Mitoxanthrone  
 CN **Mitoxantrone**  
 CN Mitozantrone  
 CN Novantron  
 CN NSC 279836  
 FS 3D CONCORD  
 DR 137635-96-2, 70945-62-9  
 MF C22 H28 N4 O6  
 CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK\*, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS\*, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU  
 (\*File contains numerically searchable property data)

Other Sources: WHO

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report  
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)  
 RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)  
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)  
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2202 REFERENCES IN FILE CA (1907 TO DATE)

79 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

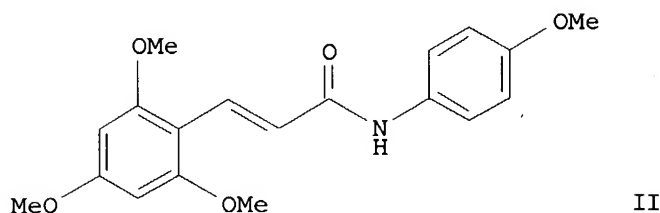
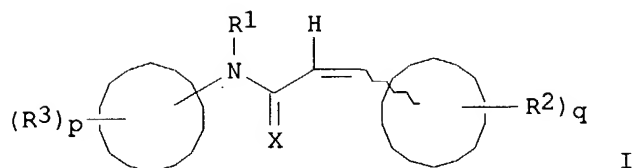
2210 REFERENCES IN FILE CAPLUS (1907 TO DATE)

# REFERENCE 1

AN 140:374987 CA  
 TI Preparation of aryl and heteroaryl propene amides as antiproliferative agents  
 IN Reddy, M. V. Ramana; Reddy, E. Premkumar  
 PA Temple University - of the Commonwealth System of Higher Education, USA  
 SO PCT Int. Appl., 165 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037751	A2	20040506	WO 2003-US26954	20030828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRAI US 2002-406766P 20020829  
 GI



AB Title compds. I [A, B = (hetero)aryl; X = O, S; R1 = sulfonylalkyl, acyl, carboxy, etc.; R2 = alkoxy, halo, CN, carboxy, carboxamido, etc.; R3 = halo, alkyl, alkoxy, CN, etc.; p = 1-3; q = 1-5] are prepared For instance, 4-methoxyphenylamino-3-oxopropanoic acid is reacted with 2,4,6-trimethoxybenzaldehyde to give II. Representative examples of activities of compds. I in cell lines (e.g., BT20, DU145) are reported. I are useful as antiproliferative agents, radioprotective agents and cytoprotective agents, including, for example, anticancer agents.

#### REFERENCE 2

AN 140:368313 CA  
 TI Dysregulation of protein kinase C activity in chemoresistant metastatic breast cancer cells  
 AU Schoendorf, Thomas; Hoopmann, Markus; Breidenbach, Martina; Rein, Daniel T.; Goehring, Uwe-Jochen; Becker, Martina; Mallmann, Peter; Kurbacher, Christian M.  
 CS Department of Natural Sciences, University of Applied Sciences, Rheinbach, Germany  
 SO Anti-Cancer Drugs (2004), 15(3), 265-268  
 CODEN: ANTDEV; ISSN: 0959-4973  
 PB Lippincott Williams & Wilkins  
 DT Journal  
 LA English  
 AB This study was performed to evaluate the role of protein kinase C (PKC) activity in the development of chemoresistance in clin. breast cancer cells. To simulate the clin. situation, native tumor cells derived from 10 patients with advanced breast cancer were brought into short-term cultures, and treated with anthracyclines (doxorubicin, mitoxantrone), paclitaxel and combinations, resp. After 3 days of incubation, we determined total PKC activity relative to each control incubated with blank medium. Furthermore, we determined the chemoresistance against these drugs from each cell population sep. Relative PKC activity ranged from 14 to 249%; 64% (37 of 58) of the breast cancer cell suspensions were considered chemoresistant. There was a non-significant trend to a higher relative PKC activity in resistant cells compared to non-resistant cells (p = 0.058), regardless of the antineoplastic agent investigated. The individual variability in both PKC activity and chemoresistance pattern revealed that dysregulated PKC activity mediates resistance to antineoplastics. To achieve clin. value, evaluation of more data

concerning the PKC signal-transduction pathway is necessary. New protocols of cancer treatment will require this information to be successful.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 3

AN 140:368312 CA  
TI Combination with liposome-entrapped, ends-modified raf antisense oligonucleotide (LErafAON) improves the anti-tumor efficacies of cisplatin, epirubicin, mitoxantrone, docetaxel and gemcitabine  
AU Pei, Jin; Zhang, Chuanbo; Gokhale, Prafulla C.; Rahman, Aquilur; Dritschilo, Anatoly; Ahmad, Imran; Kasid, Usha N.  
CS Department of Radiation Medicine, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC, USA  
SO Anti-Cancer Drugs (2004), 15(3), 243-253  
CODEN: ANTDEV; ISSN: 0959-4973  
PB Lippincott Williams & Wilkins  
DT Journal  
LA English  
AB Raf-1 protein serine/threonine kinase plays an important role in cell proliferation and cell survival. We have previously described a novel cationic liposome-entrapped formulation of raf antisense oligodeoxyribonucleotide (LErafAON) and its use as a radiosensitizer. The aim of this study was to examine the effect of combination of LErafAON and a chemotherapeutic agent on growth of human prostate (PC-3) and pancreatic tumor xenografts in athymic mice (Aspc-1 and Colo 357). In PC-3 tumor-bearing mice, administration of a combination of LErafAON (i.v., 25 mg/kg/dose, + 10/16) and cisplatin (i.v., 11.0 mg/kg/dose, + 3), epirubicin (EPI) (i.v., 9.0 mg/kg/dose, + 3) or mitoxantrone (MTO) (i.v., 2.5 mg/kg/dose, + 3) led to enhanced tumor growth inhibition as compared with single agents (LErafAON + cisplatin vs. cisplatin,  $p < 0.0002$ ,  $n = 8$ ; LErafAON + EPI vs. EPI,  $p < 0.0001$ ,  $n = 6$ ; LErafAON + MTO vs. MTO,  $p < 0.05$ ,  $n = 5$ ). In prostate or pancreatic tumor-bearing mice, combination of LErafAON (i.v., 25 mg/kg/dose, + 10/13) with docetaxel (Taxotere) (i.v., 5, 7.5 or 10 mg/kg/dose, + 2/4) led to tumor regression or enhanced growth inhibition as compared with single agents (PC-3: LErafAON + Taxotere vs. Taxotere,  $p < 0.02$ ,  $n = 7$ ; Aspc-1: LErafAON + Taxotere vs. Taxotere,  $p < 0.03$ ,  $n = 5$ ; Colo 357: LErafAON + Taxotere vs. Taxotere,  $p < 0.04$ ,  $n = 7$ ). Combination of LErafAON (i.v., 25 mg/kg/dose, + 10/13) with gemcitabine (i.v., 75 mg/kg/dose, + 4/6) also caused a significant tumor growth inhibition in the two pancreatic carcinoma models studied (Aspc-1: LErafAON + gemcitabine vs. gemcitabine,  $p < 0.0001$ ,  $n = 7$ ; Colo 357: LErafAON + gemcitabine vs. gemcitabine,  $p < 0.002$ ,  $n = 5$ ). LErafAON treatment (i.v., 25 mg/kg/dose, + 10) caused inhibition of Raf-1 protein expression in these tumor tissues (around 25-60%,  $n = 4-7$ ). Interestingly, Taxotere treatment per se also led to decreased steady state level of Raf-1 protein in PC-3 and Aspc-1 tumor tissues (i.v., 10 mg/kg/dose, + 1 or 7.5 mg/kg/dose, + 2; around 25-80%,  $n = 2/6$ ). Present studies demonstrate enhanced tumor growth inhibition or regression in response to a combination of a chemotherapeutic drug and LErafAON. These data provide a proof-of-principle for the clin. use of LErafAON in combination with chemotherapy for cancer treatment.

RE.CNT 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 4

AN 140:368289 CA  
TI The cytoplasmic trafficking of DNA topoisomerase II $\alpha$  correlates with

etoposide resistance in human myeloma cells  
AU Engel, Roxane; Valkov, Nikola I.; Gump, Jana L.; Hazlehurst, Lori; Dalton, William S.; Sullivan, Daniel M.

CS H. Lee Moffitt Cancer Center and Research Institute, Departments of Interdisciplinary Oncology and Biochemistry and Molecular Biology, Experimental Therapeutics Program, University of South Florida, Tampa, FL, 33612, USA

SO Experimental Cell Research (2004), 295(2), 421-431  
CODEN: ECREAL; ISSN: 0014-4827

PB Elsevier Science

DT Journal

LA English

AB In this study the authors have investigated the role of topoisomerase (topo) II $\alpha$  trafficking in cellular drug resistance. To accomplish this, it was necessary to sep. the influence of cell cycle, drug uptake, topo protein levels, and enzyme trafficking on drug sensitivity. Thus, the authors developed a cell model (called accelerated plateau) using human myeloma H929 cells that reproducibly translocates topo II $\alpha$  to the cytoplasm. Compared to log-phase cells, the cytoplasmic redistribution of topo II $\alpha$  in plateau-phase cells correlated with a 10-fold resistance to VP-16 and a 40-60% reduction in the number of drug-induced

double-strand DNA breaks. In addition, 7-fold more VP-16 was necessary to achieve 50% topo II $\alpha$  band depletion, suggesting that there are fewer drug-induced topo-DNA complexes formed in quiescent cells than in log-phase cells. The total cellular amount of topo II $\alpha$  and topo II $\beta$  protein in log- and plateau-phase cells was similar as determined by Western blot anal. There was a 25% reduction in S-phase cell number in plateau cells (determined by bromodeoxyuridine (BrdU) incorporation), while there was no significant difference in the equilibrium concns. of [3H]-VP-16 when log cells were compared with plateau cells. Furthermore, the nuclear/cytoplasmic ratio of topo II $\alpha$  is increased 58-fold in accelerated-plateau H929 cells treated with leptomycin B (LMB) when compared to untreated cells. It appears that the nuclear-cytoplasmic shuttling of topo II $\alpha$ , which decreases the amount of nuclear target enzyme, is a major mechanism of drug resistance to topo II inhibitors in plateau-phase myeloma cells.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 5

AN 140:368210 CA

TI Highly Altered Protein Expression Profile in the Adriamycin Resistant MCF-7 Cell Line

AU Gehrmann, Marion L.; Fenselau, Catherine; Hathout, Yetrib

CS Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, 20742, USA

SO Journal of Proteome Research (2004), 3(3), 403-409  
CODEN: JPROBS; ISSN: 1535-3893

PB American Chemical Society

DT Journal

LA English

AB The protein expression pattern in the cytosol fraction of the adriamycin resistant MCF-7 cell line (MCF-7/ADR) was compared to that of the parental MCF-7 cell line using two-dimensional gel electrophoresis and mass spectrometry. Twenty proteins with altered abundances were identified and studied in MCF-7/ADR. Both up regulation and down regulation are characterized. The most striking differences were found for proteins that were uniquely expressed in this cell line and not detectable in the parental MCF-7 cell line. These proteins include annexin I, the neuronal ubiquitin carboxyl hydrolase isoenzyme L-1 (also known as PGP9.5),

glutathione-S-transferase pi class, nicotinamide N-methyltransferase, and interleukin-18 precursor. On the other hand, catechol-O-methyltransferase was expressed in the parental cell line, but was not detected in the adriamycin resistant cell line. This protein expression pattern was unique to MCF-7/ADR and not observed in MCF-7 cell lines selected for resistant to etoposide, mitoxantrone or melphalan.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 6

AN 140:362998 CA  
TI Gamma irradiation of solid nanoparticulate active agents  
IN Lee, Robert; Hilborn, Matthew; Kline, Laura; Keller, Janine  
PA Elan Pharma International Limited, Ire.  
SO PCT Int. Appl., 79 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004032980	A1	20040422	WO 2003-US27484	20030904
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRAI US 2002-415749P 20021004

AB The present invention relates to methods for terminal sterilization of solid forms of nanoparticulate active agent compns. via gamma irradiation. The nanoparticulate active agent has an effective average particle size of less than about 2  $\mu$ , prior to incorporation into a solid form for sterilization. The resultant sterilized compns. exhibit excellent redispersibility, homogeneity, and uniformity. Also encompassed are compns. made via the described method and methods of treating animals and humans using such compns. Several examples are provided of  $\gamma$ -ray sterilization of naproxen nanoparticulate formulations. Pre-lyophilization, post-lyophilization and post- $\gamma$ -irradiation properties (particle size, stability, osmolality, pH, microbiol. testing) are described. Surface stabilizers are used.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

#### REFERENCE 7

AN 140:357355 CA  
TI Preparation of diaminothiadiaazole dioxides and monoxides as CXC- and CC-chemokine receptor ligands  
IN Taveras, Arthur G.; Chao, Jianhua; Biju, Purakkattle J.; Yu, Younong; Fine, Jay S.; Hipkin, William; Aki, Cynthia J.; Merritt, J. Robert; Li, Ge; Baldwin, John J.; Lai, Gaifa; Wu, Minglang; Hecker, Evan A.  
PA Pharmacopeia, Inc., USA  
SO PCT Int. Appl., 540 pp.  
CODEN: PIXXD2  
DT Patent

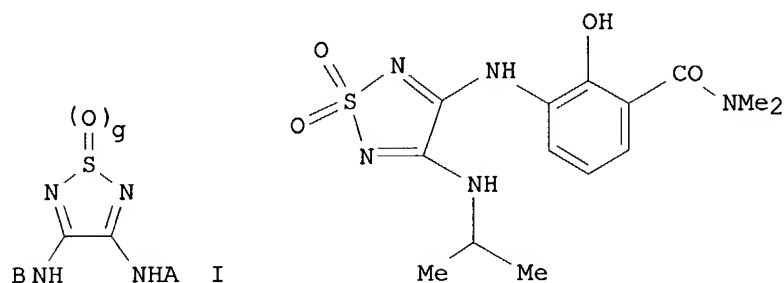
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004033440	A1	20040422	WO 2003-US31707	20031007
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRAI US 2002-417371P 20021009

GI



AB Disclosed are diaminothiadiaazole mono- and dioxides (shown as I; e.g. II) and the pharmaceutically acceptable salts and solvates thereof. Examples of substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino; examples of substituent B include aryl and heteroaryl; g = 1, 2. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 31% yield from the 4-methoxy analog and isopropylamine in the presence of DIEA in MeOH; the 4-methoxy analog was prepared from the dimethoxy analog and N,N-dimethyl-3-amino-2-hydroxybenzamide in 99% crude yield. Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

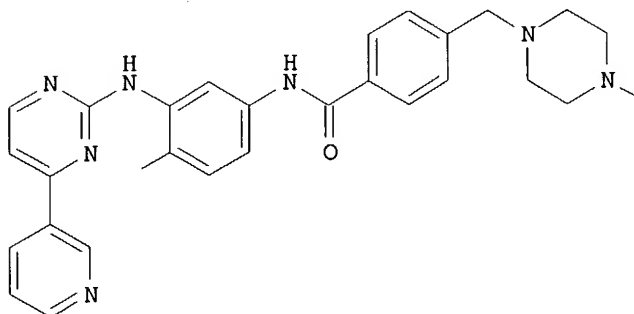
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 8.

AN 140:350542 CA  
TI Antitumor effects of imatinib (glivec, STI-571) to inhibit breast cancer resistance protein (BCRP)  
IN Houghton, Peter J.; Traxler, Peter  
PA Novartis Ag, Switz.; Novartis Pharma GmbH; St. Judes Children's Research Hospital  
SO PCT Int. Appl., 19 pp.  
CODEN: PIXXD2  
DT Patent

FAN.CNT 1

GI



T

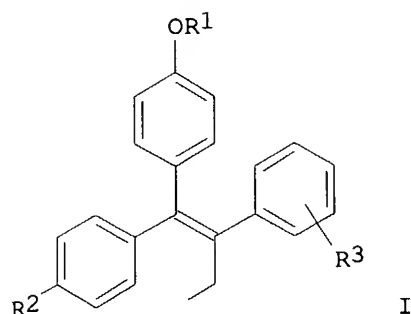
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 9

AN 140:350535 CA  
TI 1,1,2-Triphenyl-1-butene derivatives for overcoming antitumor drug  
resistance  
IN Sugimoto, Yoshikazu; Tsukahara, Satomi; Sugimoto, Yoshikazu  
PA Taiho Pharmaceutical Co., Ltd., Japan; National Cancer Center  
SO Jpn. Kokai Tokkyo Koho, 27 pp.  
CODEN: JKXXAF  
DT Patent  
LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2004123567	A2	20040422	JP 2002-286577	20020930
PRAI	JP 2002-286577	20020930			
GI					



AB 1,1,2-Triphenyl-1-butene derivs. (I; R1 = H,  $-(CH_2)_n-NR_4R_5$ ,  $-(CH)-SO_2R_4$ , with  $n = 1-4$ ,  $R_4, R_5 = H$ , alkyl;  $R_2 = OH$ , alkoxy, etc.) and their pharmaceutically acceptable salts are claimed for overcoming antitumor drug resistance from topoisomerase I and II inhibitors, including canptotecins e.g. irinotecan, topotecan, and SN-38.

#### REFERENCE 10

AN 140:350201 CA  
 TI ABCG2 overexpression in colon cancer cells resistant to SN38 and in irinotecan-treated metastases  
 AU Candeil, Laurent; Gourdier, Isabelle; Peyron, Delphine; Vezzio, Nadia; Copois, Virginie; Bibeau, Frederic; Orsetti, Beatrice; Scheffer, George L.; Ychou, Marc; Khan, Qasim A.; Pommier, Yves; Pau, Bernard; Martineau, Pierre; Del Rio, Maguy  
 CS CNRS-UMR 5160, Centre de Recherche en Cancerologie, CRLC Val d'Aurelle, Montpellier, 34298, Fr.  
 SO International Journal of Cancer (2004), 109(6), 848-854  
 CODEN: IJCNAW; ISSN: 0020-7136  
 PB Wiley-Liss, Inc.  
 DT Journal  
 LA English  
 AB Overcoming drug resistance has become an important issue in cancer chemotherapy. Among all known mechanisms that confer resistance, active efflux of chemotherapeutic agents by proteins from the ATP-binding cassette family has been extensively reported. The aim of the present study was to determine the involvement of ABCG2 in resistance to SN38 (the active metabolite of irinotecan) in colorectal cancer. By progressive exposure to increasing concns. of SN38, we isolated 2 resistant clones from the human colon carcinoma cell line HCT116. These clones were 6- and 53-fold more resistant to SN38 than the HCT116-derived sensitive clone. Topoisomerase I expression was unchanged in our resistant variants. The highest resistance level correlated with an ABCG2 amplification. This overexpression was associated with a marked decrease in the intracellular accumulation of SN38. The inhibition of ABCG2 function by Ko143 demonstrated that enhanced drug efflux from resistant cells was mediated by the activity of ABCG2 protein and confirmed that ABCG2 is directly involved in acquired resistance to SN38. Furthermore, we show, for the first time in clin. samples, that the ABCG2 mRNA content in hepatic metastases is higher after an irinotecan-based chemotherapy than in irinotecan-naive metastases. In conclusion, this study supports the potential involvement of ABCG2 in the development of irinotecan resistance in vivo.

RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT